REMARKS

Claims 1-31 will be pending in the application after introduction of the amendment. Of these claims, claims 14-27 are withdrawn from consideration on the merits subsequent to the Restriction Requirement issued on April 5, 2001. Claims 1-3 and 7-9 have been amended to address matters of form and to clarify the nature of the claimed invention. New claims 28-31 have been added. The claims, as amended, find support throughout the specification. Support for the new claims can also be found throughout the original specification, for example in originally presented claims 2, 3 and 8. Applicants respectfully submit that no new matter will be introduced into the application as filed via these amendments. Therefore, Applicants respectfully request reconsideration and allowance of pending claims 1-13 in view of the above amendments.

Claim 1 is objected for use of parenthesis in the claim. Claim 1, as amended in response to the objection, no longer contains parenthesis.

Claims 1-13 are rejected under 35 U.S.C. 112, first paragraph because the invention claimed in claims 1-13 is not commensurate in scope with enabling disclosure. This rejection is respectfully traversed.

The Examiner states, on page 3 of the rejection, that while the specification is enabled for LHRH antagonists disclosed in page 5, line 20-24, does not reasonably provide enablement for other LHRH antagonists. This rejection is respectfully traversed.

LHRH antagonists act by a reversible and competitive blockage of LHRH receptors at the pituitary. Hence, these compounds exert immediate and dose

dependent extent of hormonal suppression (LH, FSH, estrogen, progesterone). Any LHRH antagonist known for its competitive blockage of LHRH receptors at the pituitary would be suitable for the invention. It is also well within the knowledge of an ordinary artisan to determine the scope of LHRH antagonists which exhibit these characteristics, and, thus would be useful in the claimed invention without undue experimentation.

Therefore the specification provides enablement for the full scope of Claims 1-13.

Claim 3 is rejected under 35 US.C. 112, first paragraph, because the specification, while being enabling for the oral contraceptives disclosed in page 7, line 29 - page 8, line 2 does not reasonably provide enablement for other contraceptives. This rejection is respectfully traversed.

A contraceptive is disclosed as being administered to a patient for its known effects, such as prevention of ovulation and menstrual bleeding in the therapeutic interval between LHRH antagonist treatment cycles. Because the contraceptive is disclosed as being administered for its known uses, Applicants submit that any person skilled in the art would have been able to select an appropriate contraceptive from among the many known and widely used types of contraceptives such as oral, intramuscular, or subcutaneous contraceptives.

The Examiner also states that "the instant specification does not provide any working examples to point out how administration of contraceptives in combination of LHRH antagonist may be used successfully in the claimed method of treating extrauterine proliferation of endometrial tissue, chronic pelvic pain and/or fallopian

tube obstruction." The Examiner's attention is drawn to the claim language of claim 3, claiming a follow-up treatment with contraceptives. Claim 3 does not claim a combination treatment modality, i.e. administration of contraceptives in combination of LHRH antagonist, but rather, claim 3 recites a follow-up treatment modality, where a short-term induction treatment with the LHRH antagonist is followed by the administration of a contraceptive. It is, therefore, submitted that the entire scope of claim 3 is fully enabled by the disclosure.

Claim 4 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for non-steroidal anti-rheumatic agents disclosed in page 8, line 16 does not reasonably provide enablement for other non-steroidal anti-rheumatic agents. This rejection is respectfully traversed.

Similarly to claim 3, claim 4 does not claim a combination treatment, but rather, recites a follow-up treatment with non-steroidal anti-rheumatic agents between LHRH antagonist treatment cycles.

The non-steroidal anti-rheumatic agents are disclosed as suitable for treatment of pain and inflammation during the LHRH antagonist treatment-free period. Any known and approved non-steroidal anti-rheumatic agent is suitable for its known use. Therefore, one of ordinary skill in the art would have been able to select an appropriate non-steroidal anti-rheumatic agent for its known use among any known and widely used non-steroidal anti-rheumatic agents. Thus, claim 4 is fully enabled by the specification.

Claim 5 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for analgesic compounds disclosed in page 8, line

17-18 does not reasonably provide enablement for other analgesic compounds. The rejection is respectfully traversed.

Similarly to claims 3 and 4, claim 5 does not claim a combination treatment but a follow-up treatment modality with analgesics. Also similarly to claims 3 and 4, the compounds are claimed as useful in follow-up treatment, i.e., analgesics, are used for their known properties and effect of alleviating pain. Any approved analgesic in known effective doses is suitable to be given as follow-up medicine after LHRH antagonist, and choice of an analgesic would have been within the knowledge of a skilled artisan. Claim 5 is, therefore, fully enabled by the specification.

Claim 6 is rejected under 35 U.S.C, 112, first paragraph, because the specification, while being enabling for androgen compounds disclosed in page 8, line 4-8, does not reasonably provide enablement for other androgen compound agents. This rejection is respectfully traversed.

Once again, claim 6 is not drawn to a combination treatment but a follow-up treatment modality with androgens. The androgens are to be administered for their known effects. Therefore, any approved androgen is suitable for use in the present invention and would be readily identified by a person skilled in the art.

Claim 6 is, therefore, fully enabled.

Claims 2, 3, 7, 8 and 9 are rejected under 35 U.S.C. 112, second paragraph, for failing to particularly point out and distinctly claim the subject matter which applicants regard as their invention.

It is believed that all of the of the objections raised by the Examiner have been overcome by the amendment to the claims.

Claims 1-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Engel et al. (US Patent 5,633,145, hereinafter "Engel") in view of Hodgen (US Patent 5,658,884, hereinafter "Hodgen") and Nachtigall et al. (Chapter 41, Danfoth's Obstetrics and Gynecology, 1994, page 757-769, hereinafter Nachtigall). This rejection is respectfully traversed for at least the following reasons.

The Engel reference discloses a kit comprising an initial dose of an LHRH antagonist suitable for treatment of hormone dependent conditions, and at least one maintenance dose of the LHRH antagonist. The kit is suitable for a combination treatment regiment in which an initial dose is followed by several maintenance doses. In contrast, the claimed invention is drawn to a short term induction for a short time period, after which the administration of the LHRH antagonist is stopped. As stated by the Examiner, the reference does not specify either the time period or frequency of administration or the amounts of the LHRH antagonist to achieve the estrogen serum level of between 35 and 80 pg/ml. Further, the reference does not teach or suggest any follow-up treatment or therapy with progestine/gestagens or androgens for further prevention of ovulation besides menstrual and endometrial bleeding to avoid re-occurrence of symptoms or new endometric. Additionally, an immediate follow-up therapy with non-steroidal anti-rheumatic agents or analgesics is also not disclosed or suggested in the Engel reference.

To cure the deficiencies of the Engel reference, the Examiner cited the Hodgen reference as teaching administration of the GnRH antagonist such that the estrogen level between 35 and 45 pg/ml is achieved. Hodgen does disclose that a 24 hour serum estradiol level in the range of 35 to 45 pg/ml can be achieved in monkeys by

administering LHRH antagonist. However, Hodgen does not give any dose range of the LHRH antagonist. The dose has to be determined according to the results of an expensive and time consuming progesterone challenge test. Furthermore, the Hodgen invention is directed to long-term treatment intervals, such as a number of years of therapy. See column 9, lines 3-6. The teachings of the reference do not suggest applicability of the long-term treatment study conducted on primates to a short-term treatment regiments. No suggestion that an effective therapeutic management of extrauterine proliferation of endometrial tissue, chronic pelvic pain and/or fallopian tube obstruction may be achieved by a short 4-to 12 week induction treatment can be found in the reference. Moreover, similarly to the Engel reference, Hodgen does not disclose any combination therapy. It is, therefore, submitted that the Engel and Hodgen references alone or in combination do not teach or fairly suggest a method of therapeutic management of extrauterine proliferation of endometrial tissue, chronic pelvic pain and/or fallopian tube obstruction by administration of an LHRH antagonist for a short term induction treatment for a period of about 4 to 12 weeks, and subsequently completely ceasing the administration of the LHRH antagonist.

The Examiner further cites Nachtigall as teaching use of Danazol, an oral contraceptive, for treatment of endometriosis. Once again, nothing in this reference suggests the claimed method, involving administering to a patient of LHRH antagonist for a short-term induction period. Furthermore, while Danazol is useful in treating endometriosis, due to the occurrence of severe side effects, it is common knowledge that treatment of endometriosis with Danazol has been largely abandoned nowadays.

Oral contraceptives do not cure endometriosis. As disclosed on page 766, column 1, last paragraph of Nachtigall, "there are few data to support the use of this class of drugs. No controlled or comparative trials have been performed to confirm efficacy, making this treatment approach at least acceptable of the medical therapies available." The reference, therefore, teaches away from use of oral contraceptives in treatment of endometriosis.

Non-steroidal anti-rheumatic agents and analgesics are discussed for the treatment of pain as well as of inflammation. e.g., of patients with chronic adhesions or with low grade stages of the disease. These agents are not effective in curing patients with severe or chronic endometriosis, not even in the short term.

The Examiner further states that it is prima facie obvious to combine agents, each of which is taught by the prior art for the same purpose, in order to form a combination to be used for the same very purpose. It is well known in the art of therapeutical treatment of patients, that combining pharmaceutical agents can not be done freely, even if they are known for the same purposes. Combination of pharmaceuticals often leads to serious side effects due to their potential interaction. Moreover, as discussed above, the invention is not drawn to a combinatorial treatment, but rather to a follow-up treatment, and, therefore, the reasons for combining agents given by the Examiner are simply not applicable to the claimed invention. Also, according to the Examiner's statement, optimization of parameters, such as dosage range, dosage frequency, and timing is obvious as being within the skill of the artisan. While routine minor adjustments of dosage and its frequency may well be within the skill of an ordinary artisan, reduction of treatment time from years of therapy as taught

Oral contraceptives do not cure endometriosis. As disclosed on page 766, column 1, last paragraph of Nachtigall, "there are few data to support the use of this class of drugs. No controlled or comparative trials have been performed to confirm efficacy, making this treatment approach at least acceptable of the medical therapies available." The reference, therefore, teaches away from use of oral contraceptives in treatment of endometriosis.

Non-steroidal anti-rheumatic agents and analgesics are discussed for the treatment of pain as well as of inflammation. e.g., of patients with chronic adhesions or with low grade stages of the disease. These agents are not effective in curing patients with severe or chronic endometriosis, not even in the short term.

The Examiner further states that it is prima facie obvious to combine agents, each of which is taught by the prior art for the same purpose, in order to form a combination to be used for the same very purpose. It is well known in the art of therapeutical treatment of patients, that combining pharmaceutical agents can not be done freely, even if they are known for the same purposes. Combination of pharmaceuticals often leads to serious side effects due to their potential interaction. Moreover, as discussed above, the invention is not drawn to a combinatorial treatment, but rather to a follow-up treatment, and, therefore, the reasons for combining agents given by the Examiner are simply not applicable to the claimed invention. Also, according to the Examiner's statement, optimization of parameters, such as dosage range, dosage frequency, and timing is obvious as being within the skill of the artisan. While routine minor adjustments of dosage and its frequency may well be within the skill of an ordinary artisan, reduction of treatment time from years of therapy as taught

by the references to a maximum of three month periods, as claimed in the instant invention, can hardly fall within the meaning of "optimization". In fact, modifying the treatment regiments disclosed in the cited references to shorten them to 4 to 12 week induction treatments would render the treatment regimens disclosed in Engel and Hodgen unsatisfactory and non-useful for the intended therapeutic treatments.

It is, therefore, submitted that the references alone or in combination do not suggest the claimed therapeutic management of extrauterine proliferation of endometrial tissue, chronic pelvic pain and/or fallopian tube obstruction by administration of an LHRH antagonist in the form of a short term induction treatment for a period of about 4 to 12 weeks to a patient in need of such treatment with subsequent termination of LHRH antagonist administration.

In view of the foregoing, Applicants respectfully submit that the application is in condition for allowance. Notification to that effect is respectfully requested. Should questions relating to patentability remain, the Examiner is invited to contact the undersigned to discuss the same.

Respectfully submitted,

PILLSBURY WINTHROP LLP

By _____

Irina S. Zemel, Ph.D.
Reg. No. 43,402
Blair Elizabeth Taylor, Ph.D.
Reg. No. 44,370
Tel. No.: (703) 905-2227
Fax No.: (703) 905-2500

Attachment: Appendix

1600 Tysons Boulevard
McLean, VA 22102
(703) 905-2000

APPENDIX

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Claims 1-3 and 7-9 are amended as follows:

1. (Amended) In the method of therapeutic management of extrauterine proliferation of endometrial tissue, chronic pelvic pain and/or fallopian tube obstruction [(FTO)], the improvement consisting of administration of an LHRH antagonist in the form of a short term induction treatment for a period of about 4 to 12 weeks to a patient in need of such treatment, whereby subsequently the administration of the LHRH antagonist is ceased.

2. (Amended) A method according to claim 1 wherein the LHRH antagonist is administered [such that] in a dosage to achieve the estrogen serum concentration level [is] between about 35 pg/ml and about 80 pg/ml[, preferably between about 45-75 pg/ml, more preferably about 50-75 pg/ml].

3. (Amended) A method according to claim 1 wherein the short-term induction treatment with the LHRH antagonist is followed by administration of a contraceptive[, preferably an oral contraceptive].

7. (Amended) A method according to claim 1 wherein the short-term induction treatment with the LHRH antagonist is followed by the combined or separate administration of one or more active agents selected from the group consisting of a

contraceptive, [preferably an oral contraceptive,] a non-steroidal anti-rheumatic agent, an analgesic, an androgen other than a 17-alpha-alkyl substituted testosterone or any combinations thereof.

8. (Amended) A method according to claim 1 wherein the LHRH antagonist is administered starting in the early to mid follicular phase[, preferably on cycle day one to three].

9. (Amended) A method according to claim 1 wherein the LHRH antagonist is selected from the group consisting of cetrorelix, teverelix, ganirelix, antide, abarelix and [D-63153] Ac-D-Nal-D-pCl-Phe-D-Pal-Ser-N-Me-Tyr-D-Hci-Nle-Arg-Pro-D-Ala-NH2 LRHR antagonist.

New claims 28 -31 are added.